REMARKS

Claims 1-9 and 14-18 are pending in this application. Claims 1-9 and 14-18 stand rejected. No claims are objected to. Applicant has herein has amended claims 3 and 8. Support for amended claims can be found on pages 26-30 of the specification as well as the sequence listing. Thus, no new matter has been added.

Rejections Withdrawn

The amendment filed on 3/3/03 has been considered by the Examiner was found to be persuasive-in-part. Rejection of claims 17-18 under 35 U.S.C. § 112, first paragraph is withdrawn in view of Applicants' amendment. Rejection of claims 1-9 under 35 U.S.C. § 112, first paragraph is withdrawn in view of Applicants' amendment. All art rejections are withdrawn in view of Applicants' arguments.

Rejection under 35 U.S.C. §112, first paragraph

Claim 3 remains rejected under 35 U.S.C. § 112, first paragraph for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. In particular, the Examiner alleges that reference to the deposit information found at page 32 of the specification is insufficient. The Examiner alleges that a declaration by applicant or assignee or a statement by an attorney of record stating that the deposit has been made is required.

Applicants respectfully traverse this rejection. As noted in the previous response, monoclonal antibody 6A1 is produced by the hybridoma 3426A11C1B9, which was deposited October 6, 1993 with the European Collection of Animal Cell Cultures (ECACC), Public Health Laboratory Service Centre for Applied Microbiology and Research, Porton

Down, Salisbury, Wiltshire, SP4 OJG United Kingdom under accession No. 93100620. This information is disclosed on page 32 of the specification. Pursuant to 37 C.F.R. § 1.808(a), it is hereby stated that subject to 37 C.F.R. §1.808(a), all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application.

Furthermore, the rules regarding the deposit of biological materials clearly state that a deposit is not necessary if the biological materials are "known and readily available to the public or can be made or isolated without undue experimentation". (See 37 C.F.R. § 1.802 and MPEP Chapter 2400.) It is submitted that one of skill in the art would, in light of the teachings in the specification, be enabled to make and use the monoclonal antibodies of the present invention, including 6A1 and 3B9, without undue experimentation. The specification provides sufficient disclosure relating to these antibodies for one of skill in the art to make and use the claimed antibodies. For example, Applicants have provided the CDRs for monoclonal antibody 3B9 and a description of how to construct a monoclonal antibody using these CDRs (see pages 26-30 of the specification). As such, claim 3 has been amended herein to include 3B9 as it did when originally filed. It is submitted that claim 3 is fully enabled by the specification and therefore, it is respectfully requested that this rejection be withdrawn.

In light of the above arguments, it is respectfully requested that the rejections under 35 U.S.C. § 112, first paragraph be withdrawn.

Double Patenting

Claims 1-9 and 17-18 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-18 and 28-29 and 34-35 of U.S. Patent No. 5914110.

As was noted in the previous response, should it be determined that a terminal disclaimer is necessary after allowable subject matter has been agreed, Applicants will timely file such disclaimer.

Rejection under 35 U.S.C. §112, second paragraph

Claim 8 remains rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner notes that the first amino acid of SEQ ID NO. 16 should be lys not leu, as it was disclosed in the Sequence Listing.

Applicants apologize for the error in SEQ ID NO:16 in claim 8. Applicants herein have amended claim 8 so that the first amino acid of SEQ ID NO:16 is now lys not leu, therefore, rendering this rejection moot.

Rejection under 35 U.S.C. § 103

Claims 1-4 and 14-18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Queen, *et al.* WO 90/07861 in view of Co, *et al.*, *Nature,* Vol. 351 p. 501 (1991), Abrams, *et al.* US 5041381, Chreiten, *et al., J. Immunol Methods,* Vol. 117 p. 67 (1991), Curtis, *et al.* US 5108910, Orlandi, *et al., PNAS,* Vol. 86 p. 3833 (1989), JP-327725, Coffman, *et al.* WO 89/06975 and Maggio, *Enzyme-Immunoassay* CRC Press Inc. 1980 pp. 167-178.

Specifically, the Examiner alleges that Queen, *et al.* disclose a method for producing fusion proteins which are chimeric or CDR-grafted, humanized antibodies. In particular, the Examiner alleges that Queen, *et al.* disclose an approach to producing CDR-grafted antibodies which involves the selection of human variable regions which are homologous to the murine variable region to be humanized and computer modeling to identify murine

framework residues which make key contacts with CDRs, which are then introduced into human framework (see abstract, p. 4-6, and 10-11). In addition, the Examiner alleges that Co, *et al.* disclose that the art recognizes that humanized antibodies are expected to have advantage for use in *in vivo* human therapy.

The Examiner alleges that in view of Orlandi, *et al.*, "it would have been obvious to one of ordinary skill in the art at the time of the applicant's invention to clone and sequence the hybridoma of the mouse monoclonal antibodies to IL-4 which have neutralizing activity." The Examiner alleges that a large portion of such antibodies would have been expected to have dissociation constants of 2×10^{-10} or less. The Examiner goes on to allege that having obtained murine neutralizing antibodies and cloning and sequencing them, it would have been obvious to use methods taught by Queen, *et al.* to develop fusion proteins which are chimeric antibodies having murine variable regions and human constant regions of humanized antibodies comprised of mouse CDRs fused to framework sequences derived from human antibodies having variable regions with high homology to the murine antibodies. The Examiner also alleges that it would have been further obvious to include pharmaceutically acceptable carrier as taught by Abrams, *et al.* and a second fusion taught by Curtis, *et al.* and screen for high affinity antibodies as taught by Maggio. The Examiner also alleges that it would have been obvious to one of skill in the art to produce the claimed antibodies in view of the teaching of Coffman, *et al.* that blocking antibodies specific for IL-4 had the potential to reduce IgE response together with the advantages discussed by Co, *et al.*

Applicants respectfully traverse this rejection. For a proper obviousness rejection under 35 U.S.C. 103, the Examiner has the burden of establishing prima facie with evidence or reasons that, *inter alia*, at the time of the invention, (1) the prior art of record would have suggested or motivated one of ordinary skill in the art to carry out the combination and

modification of the prior art as suggested by the Examiner to arrive at the claimed invention, and (2) "the prior art would also have revealed that in so making or carrying out, those of ordinary skill in the art would have a reasonable expectation of success. Both the suggestion [or motivation] and the reasonable expectation of success must be founded in the prior art, not in the appellants' disclosure." *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991) (citations omitted).

Further, any teaching which could be had from the prior art would not put one of skill in the art in possession of the antibodies and constructs as claimed. Contrary to the Examiner's arguments, the statutory standard of §103 is whether the invention, considered as a whole, would have been obvious to one skill in the art, not whether it would have been obvious to one skilled in the art to try various combinations. *N.V. Akzo v. E.I. duPont de Nemours & Co.*, 1 USPQ2d 1704 (Fed Cir 1987). It is clear that it is improper to reject claims as "obvious to try" where the motivation to combine the references arises merely because the subject of the claimed invention is a promising field for experimentation. The instant rejection falls within this category. The applicants' invention cannot be rejected as obvious where the prior art provides only general guidance as to the particular form of the claimed invention or how to achieve it. *In re O'Farrell*, 7 USPQ2d 1673 (Fed Cir 1988).

Applicants respectfully submit that as presented in response to the previous Office Action, the Examiner has presented no evidence that a large portion of mouse monoclonal antibodies to human IL-4 would demonstrate a dissociation constant of 2×10^{-10} or less. Moreover, even assuming, *arguendo*, that the Examiner's asserted teachings could be had from the cited references, there is still no suggestion or teaching in the prior art of a high affinity antibody which is specific for IL4 or the specific antibody constructs, as claimed by the Applicants.

None of the cited references, either alone or in combination, teach or suggest an antibody with a dissociation constant equal to or less than 2×10^{-10}. Queen, *et al.* merely suggest methods for humanizing monoclonal antibodies from a non-human species. They do not teach or suggest the use of these methods on rodent antibodies raised specifically against human IL-4 to provide monoclonal antibodies with high binding affinity. Similarly, Co, *et al.* disclose general advantages of humanizing monoclonal antibodies raised in mice for reducing immunogenicity in humans However, they do not specifically discuss humanizing monoclonal antibodies against human IL-4.

Abrams, *et al.* and JP-327725 merely disclose mouse monoclonal antibodies specific for human IL-4. However, neither reference teaches or suggests creating a chimeric monoclonal antibodies against human IL-4 with a high binding affinity. The Examiner alleges that Abrams, *et al.* suggest "that neutralizing anti-IL-4 antibodies have potential therapeutic utility." Applicants respectfully submit that Abrams, *et al.* do not teach or suggest that monoclonal antibodies raised in rodents against human IL-4 would be expected to have a high binding affinity and/or therapeutic effect if humanized.

Similarly, Coffman, *et al.* merely proposes a therapeutic effect of administering an antagonist to human IL-4 such as an antibody. They do not teach or suggest chimeric monoclonal antibodies against human IL-4 with a high binding affinity for IL-4.

Furthermore, Curtis, *et al.* merely disclose an amino acid sequence of a fusion protein linked to an additional peptide where GM-CSF is fused to IL-3. The Examiner alleges the Curtis, *et al.* states that the peptide of their invention is highly antigenic and provides epitope reversible bound by a specific monoclonal antibody. However, Curtis, *et al.* do not suggest that creating a fusion protein of humanized rodent monoclonal antibody against IL-4 with a second fusion element will have a high binding affinity. Applicants respectfully submit that

the teaching of Curtis, *et al.* are directed specifically to GM-CSF fused to IL-3 and the advantages thereof. They do not teach or suggest that fusion of other peptides will have the same synergistic effect.

Maggio is limited to a teaching of general immunoassay procedures. Maggio fails to teach or suggest a high affinity antibody or, as asserted by the examiner, that most antibodies have such a high affinity. Similarly, Cretien, *et al.* teach anti-IL-4 rat mAb 11B4 which is used in immunoenzymatic assay and immunopurification.

Newly cited reference Orlandi, *et al.* merely discloses method of using primers for V domains of mouse immunoglobulin heavy and light chain for forced cloning and amplification mouse hybridomas. However, the reference does not teach or suggest that the method could be used to produce humanized antibodies from mice against human IL-4 with a high binding affinity. The reference merely provides oligonucleotide primers used in PCR reactions to amplify heavy and light chain variable regions from mouse monoclonal antibodies. The reference is an invitation to the skilled artisan to "try" to produce V domains from mouse immunoglobulins for cloning. It does not teach or suggest, alone or in combination with the other cited references, that a fusion protein against human IL-4 will have a high binding affinity or will be therapeutically valuable.

Applicants respectfully submit that in view of the forgoing remarks, Applicants have overcome the Examiner's rejection of claims under 35 U.S.C. §103(a), and that this rejection should be withdrawn.

Applicants reserve the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the specification. Applicants thank the Examiner for the Office Action and

believes this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration and allowance of the pending claims is earnestly solicited.

If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicants' undersigned agent.

Respectfully submitted,

Andrea V. Lockenour
Attorney for Applicants
Registration No. 51,962

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-7568
Facsimile (610) 270-5090
n:\avl\patapps\p50186-2xC2amendment2003.doc